PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between macronutrient intake and cognition in individuals aged under 65 in China: A cross sectional study
AUTHORS	Ding, Bingjie; Zhang, Yong; Zhao, Lei; Bi, Yanxia; Xiao, Rong; Ma, Weiwei

VERSION 1 – REVIEW

REVIEWER	Stephanie Oleson University of Texas at Austin, United States.
REVIEW RETURNED	02-Aug-2017

GENERAL COMMENTS	Overall, the authors set out to address an important research question in investigating the role that macronutrients play in cognitive function. However, there are a number of areas that need to be addressed: The researchers state that participants were divided into 3 different age groups (<45 years, 45-55 years, and > 55 years), but do not list total age range. This should be reported somewhere. It would be particularly helpful to see the total age range of those with MCI. The title of the manuscript, “The Association between Macronutrients Intake with Mild Cognitive Impairment in Young and Middle-Aged Chinese Population” implies that macronutrient and MCI associations may be compared between young and middle-aged groups, but it seems unlikely there were a large number of “young” MCI participants, given that there were 80 total. It is unclear how presence of hyperlipidemia for participants was determined in this study. In the Dietary Questionnaire section on page 7, it is unclear how “food models such as special charts and measuring rulers and cups” were utilized to aid with FFQ. Can this be elaborated? Can you also elaborate on how the dietary interviewer aided with data collection? In the Subject paragraph on pg 8, it says “In addition, age, BMI, education, hypertension, and hyperlipidemia were associated with higher risk of MCI.” It seems like it should be specified that greater age and BMI, and presence of hypertension and hyperlipidemia were associated with greater risk for MCI, while education was negatively associated with risk for MCI. On page 8, the line, “However, no significant differences in the prevalence of MCI were discovered in subjects among groups with different gender, race/ethnicity, labor intensity, aerobic exercise, smoking, drinking, and diabetic status” is unclear.

	In the first paragraph on page 9, hyperlipidemia and total energy intake are referred to as “risk factors” for MCI. Based on the study methods, it seems inaccurate to refer to these as risk factors. It just seems they are associated with the presence of MCI. This should be re-worded. When comparing the current study results to that of Robert et al., it was mentioned that dietary carbohydrates in the current study were mainly derived from rice and wheat flour. Can information regarding simple sugars versus complex carbohydrates be reported? It may be helpful to have this information in a table if it is available. At the end of the first paragraph on page 10, it is stated that glucose and insulin metabolism is less likely to be affected by long chain carbohydrates in younger adults. Can the authors elaborate on why this would be the case? Additionally, it seems important to acknowledge that there were only 7 adults in the highest carbohydrate quartile. When reporting associations between dietary fat and cognition from previous literature in the discussion on page 10, it would be important to specify the dietary fat composition for these studies. For example, in Holloway et al. (2011), did the high fat diet primarily consist of saturated fat? Or other types of fat? Similarly, is it possible to report the breakdown of dietary fat consumption in the present study (e.g., saturated fat, polyunsaturated fat, monounsaturated fat, etc)? It also seems worthwhile to add some discussion regarding the role that hyperlipidemia may play in cognitive function in the context of a high-fat diet. Waist/hip ratio for participants in the current study is referenced in the first paragraph on page 11, but the authors do not report the data. Can this be reported? If not, it seems unnecessary to make this reference. The description of the high fat/high protein diet as a “risk factor” of MCI seems like it should be toned down. Since this study is cross-sectional, the only conclusion that can be drawn is that this dietary pattern is associated with the presence of MCI. Furthermore, there is no discussion for why high protein consumption is associated with MCI. This should also be discussed in the context of the high fat diet. Overall, there are many grammatical errors throughout the manuscript that need to be addressed. It would significantly benefit from proofreading.

REVIEWER	Rosilene Ribeiro The University of Sydney, Australia
REVIEW RETURNED	10-Sep-2017

GENERAL COMMENTS	The Association of Macronutrients Intake with Mild Cognitive Impairment in Young and Middle-Aged Chinese Population Overall comments: The manuscript contains several syntactical and grammatical errors readily rectified with further more careful proof reading. You should also add reference to any methods/grouping used. Introduction Please add reference to sentence on pg. 5 line 5-6 Data collection Please specify and explain what methods were used to collect physical and laboratory parameters. Please be more specific about what races the groups were divided into. Please add reference to BMI categories. Regarding the BMI cut-off used: Recent research have shown and proposed a different cut-off for Asian population, please consider using a different BMI cut-off in your analysis as the current cut-off may not be appropriate for the group being studied. Please either explain your rationale for education grouping or add reference to it. Please do the same for physical activity and add some more information regarding how the data was collected (i.e. questionnaire, pedometer etc). Dietary questionnaire Please add reference to FFQ used. Also, had this questionnaire been validated in this age group? Cognitive function screening for MCI Please make sure all abbreviations used have been explained/fully written the first time it appears in manuscript (apart from abstract), e.g. MoCA, MMSE Statistical analysis Please be clear as to why categorical data was presented as mean or median. Results Please reword sentence on line 55-56 of page 6 as I am not sure if I understand it. Tables should have enough information to stand alone, this is not the case at the moment as there are several essential information missing in tables eg Table 1- race/ethnicity ‘Han” and ‘other’ Table 2 – title should be more informative i.e. %fat in relation to what? Why are the groups divided into quartiles of %fat and %fat itself is also in the table?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Stephanie Oleson
Institution and Country: University of Texas at Austin, United States.
Please state any competing interests: None declared
Please leave your comments for the authors below
Overall, the authors set out to address an important research question in investigating the role that macronutrients play in cognitive function. However, there are a number of areas that need to be addressed:

1. The researchers state that participants were divided into 3 different age groups (<45 years, 45-55 years, and > 55 years), but do not list total age range. This should be reported somewhere. It would be particularly helpful to see the total age range of those with MCI. The title of the manuscript, "The Association between Macronutrients Intake with Mild Cognitive Impairment in Young and Middle-Aged Chinese Population" implies that macronutrient and MCI associations may be compared between young and middle-aged groups, but it seems unlikely there were a large number of "young" MCI participants, given that there were 80 total.
Answer: Thank you for your valuable questions. We added the age range (30~64 years) of the subjects (See page 8 line 45). We also rewritten the title of the manuscript as "The Association of Macronutrients Intake with Mild Cognitive Impairment in age<65 Chinese Population". (See the title page line 3-4)

2. It is unclear how presence of hyperlipidemia for participants was determined in this study.
Answer: Thank you for your question. To measure the blood lipid levels of the participants, blood samples were collected and tested for total cholesterol and triglyceride with an automatic biochemistry analyzer (Olympus, AU 400, Japan). Hyperlipidemia was defined as hypercholesterolemia (Serum cholesterol>5.2mmol/L) and/or hypertriglyceridemia (Serum triglyceride>1.7 mmol/L). We have added this to the materials and methods section. (See page 6 line 41-47)

3. In the Dietary Questionnaire section on page 7, it is unclear how "food models such as special charts and measuring rulers and cups" were utilized to aid with FFQ. Can this be elaborated? Can you also elaborate on how the dietary interviewer aided with data collection?
Answer: These are very good questions. The following images represent some of the food models, such as rice, steamed bread, soy milk, orange and green beans. Each food model shows its weight. The participant could find their foods and quantity by pointing to the corresponding models, we therefore could calculate the relatively accurate food intake of the subjects per day. Dietary interviewers were nurses at community hospitals trained by dietitians, and they obtained food intakes of participants per day aided by food models and filled in the dietary questionnaire.

4. In the Subject paragraph on pg 8, it says "In addition, age, BMI, education, hypertension, and hyperlipidemia were associated with higher risk of MCI." It seems like it should be specified that greater age and BMI, and presence of hypertension and hyperlipidemia were associated with greater risk for MCI, while education was negatively associated with risk for MCI.
Answer: Thank you for your valuable suggestions. We have revised this section according to your suggestion to make the statement more specific and clear. (See page 8 line 49-52)

5. On page 8, the line, “However, no significant differences in the prevalence of MCI were discovered in subjects among groups with different gender, race/ethnicity, labor intensity, aerobic exercise, smoking, drinking, and diabetic status” is unclear.
Answer: Thank you for your suggestion. We have re-written this sentence to make it clearer. (See page 8 line 52-56).

6. In the first paragraph on page 9, hyperlipidemia and total energy intake are referred to as “risk factors” for MCI. Based on the study methods, it seems inaccurate to refer to these as risk factors. It just seems they are associated with the presence of MCI. This should be re-worded.
Answer: Thank you for your suggestion. We have revised the paragraph in the manuscript according to your suggestion. (See page 9 line 34-43.)

7. When comparing the current study results to that of Robert et al., it was mentioned that dietary carbohydrates in the current study were mainly derived from rice and wheat flour. Can information regarding simple sugars versus complex carbohydrates be reported? It may be helpful to have this information in a table if it is available.
Answer: Thank you for your questions. Chinese diets are rich in starchy foods (e.g., refined grain, tubers and their products), which represent the main source of our dietary energy. According to the Chinese Nutritional Guidelines, carbohydrates should contribute 55–65% of the daily energy intake. We hypothesized that the different dietary pattern might partially explain why our results were different from that of Robert et al. because the effect of simple sugars and complex carbohydrates on health is completely different. Instead of adding a table comparing the simple sugars and complex carbohydrates, we list a reference which has good discussion on this topic.
Suter PM. Carbohydrates and dietary fiber. Handb Exp Pharmacol. 2005;(170):231-61.

8. At the end of the first paragraph on page 10, it is stated that glucose and insulin metabolism is less likely to be affected by long chain carbohydrates in younger adults. Can the authors elaborate on why this would be the case? Additionally, it seems important to acknowledge that there were only 7 adults in the highest carbohydrate quartile.
Answer: Thank you for your questions. When comparing the results of this study to that of Robert et al., we found that high carbohydrate intake was negatively associated with the risk of MCI. We then tried to explore the underlying mechanisms for this difference. We found that the age of the participants in these two studies was significantly different. As we know, islet function is declined with aging, and the elderly are prone to have abnormal glucose metabolism if they intake more simple sugar. In Robert et al. study high carbohydrate were mainly from simple sugar, which was the risk factor of MCI in the elderly (median age was 79.5 years). However, in our study, the participants were relatively younger (48.5±7.3 years). Although 29.5% of participant had diabetes, but the islet function of the whole cohort should still be better than that of the participants in Robert et al. study. Therefore, even if they eat more staple food, the risk of abnormal blood glucose was relatively small. This is why we stated that glucose and insulin metabolism was less likely to be affected by long chain carbohydrates in younger adults. However, the above statement is just our hypotheses, which need to be proved by experimental studies. It seems that this hypothesis was very premature and caused misunderstanding; we therefore re-wrote the discussion section. (see page 10 line 34-49).
There were 166 participants in the highest carbohydrate quartile, but only 7 had MCI (4.2%). The prevalence of MCI in this group was lower than other groups. This is consistent with the main finding of the present study that the MCI prevalence was negatively correlated with high carbohydrate intake (see table 4).

9. When reporting associations between dietary fat and cognition from previous literature in the discussion on page 10, it would be important to specify the dietary fat composition for these studies. For example, in Holloway et al. (2011), did the high fat diet primarily consist of saturated fat? Or other types of fat?
Answer: Thank you for your questions. Holloway et al. (2011) did not report the consists of fat in their study. They only stated that high fat diet in their study was consisting of 70% fat, 4% carbohydrates and 26% protein. Another reference, Edwards LM (2011) also didn't report the consist of fat in their study, which state Calories derived from fats in the high-fat diet comprised 74% of total intake and calories from carbohydrates only 2%.

10. Similarly, is it possible to report the breakdown of dietary fat consumption in the present study (e.g., saturated fat, polyunsaturated fat, monounsaturated fat, etc)?
Answer: Thank you for your valuable advice. In the dietary questionnaire, the types of cooking oil, such as Olive oil, Peanut oil and Linseed oil, was not recorded, so it is impossible to precisely report the breakdown of dietary fat consumption in the present study. We will improve our questionnaire in future studies to acquire more complete information of dietary fat intake to further investigate the relationship between specific fatty acids and cognitive function.

11. It also seems worthwhile to add some discussion regarding the role that hyperlipidemia may play in cognitive function in the context of a high-fat diet.
Answer: Thank you for your suggestion. We have added the discussion regarding the roles of hyperlipidemia in cognitive dysfunction in the context of a high-fat diet. (See page 11 line 28-39).

12. Waist/hip ratio for participants in the current study is referenced in the first paragraph on page 11, but the authors do not report the data. Can this be reported? If not, it seems unnecessary to make this reference.
Answer: Thank you very much. We have added the data into table 1 and table 2.

13. The description of the high fat/high protein diet as a "risk factor" of MCI seems like it should be toned down. Since this study is cross-sectional, the only conclusion that can be drawn is that this dietary pattern is associated with the presence of MCI.
Answer: Thank you for your suggestion. We have re-written the conclusion to emphasize the association rather than the causing effect of high fat/high protein diet on MCI. (See page 12 line 52-55).

14. Furthermore, there is no discussion for why high protein consumption is associated with MCI. This should also be discussed in the context of the high fat diet.
Answer: Thanks for your valuable suggestion. We have added some discussion on the potential role(s) of high protein consumption in MCI in the context of a high-fat diet. (See page 11 line 41-56).

15. Overall, there are many grammatical errors throughout the manuscript that need to be addressed. It would significantly benefit from proofreading.
Answer: Thank you very much. We have corrected the grammatical errors throughout the manuscript and marked these changes in marked copy.

Reviewer: 2
Reviewer Name: Rosilene Ribeiro
Institution and Country: The University of Sydney, Australia
Please state any competing interests: None declared
Please leave your comments for the authors below
The Association of Macronutrients Intake with Mild Cognitive Impairment in Young and Middle-Aged Chinese Population

1. Overall comments:
The manuscript contains several syntactical and grammatical errors readily rectified with further more careful proof reading. You should also add reference to any methods/grouping used.
Answer: Thank you very much. We have corrected the grammatical errors throughout the manuscript and marked these changes in marked copy.

2. Introduction
Please add reference to sentence on page 5 line 5-6
Answer: Thank you for your suggestion. We have added a reference to this sentence. (See page 5 line 5-7).

3. Data collection
Please specify and explain what methods were used to collect physical and laboratory parameters.
Answer: Thank you very much. We have specified what methods were used to collect physical and laboratory parameters in the manuscript, which was marked in marked copy. Please see “Data collection and grouping” on page 6 line26-34 on the revised manuscript.
4. Please be more specific about what races the groups were divided into.
Answer: Thanks for your advice. Because the race of most participants was Han, we divided the subjects into two groups, Han and other. “Other” included all races except Han, such as Manchu, Hui, Koreans, Mongols and so on.

5. Please add reference to BMI categories. Regarding the BMI cut-off used: Recent research have shown and proposed a different cut-off for Asian population, please consider using a different BMI cut-off in your analysis as the current cut-off may not be appropriate for the group being studied.
Answer: Thank you for your valuable suggestion. We have added a reference to the current BMI categories. (see page 6 line 52). In order to compare to western studies, we used the WHO BMI cut-off (normal<25kg/m2, overweight 25-29.9kg/m2, obese >30 kg/m2) in our study. In fact, we have analyzed the data by using the WHO Asian specific BMI cut-off, and the main results have no obvious difference from the current result (see the table below). Therefore, we would like to use WHO BMI cut-off in the present study, and we may use the BMI cut-off specific for Asians in future studies.

Table 4 association of% macronutrient (carbohydrates, fat, and protein) with incident MCI (Asian specific BMI cut-off)
Variable
Cutpoint(%)
Incident MCI,N(%)
OR(95%CI)a
P
Carbohydrate

Q1
<46
33(20.0)
reference

Q2
47-54
25(15.2)
0.76(0.41-1.38)
0.36
Q3
55-63
15(9.1)
0.57(0.28-1.13)
0.11
Q4
>63
7(4.2)
0.30(0.12-0.72)
0.007
Protein

Q1
<14.9
10(6.1)
reference

Q2
15.0-16.5
20(12.1)
1.70(0.74-3.93)
0.21
Q3
16.6-18.5
23(13.9)
2.41(1.07-5.44)
0.03
Q4
>18.5
27(16.3)
2.71(1.22-6.02)
0.01
Fat

Q1
<20
6(3.6)
reference

Q2
21-28
14(8.5)
2.14(0.78-5.87)
0.12
Q3
29-35
28(17.0)
3.32(1.29-8.56)
0.01
Q4
>35
32(19.3)
3.98(1.57-10.13)
0.004
Abbreviations: CI, confidence interval; OR,odds ratio; MCI, mild cognitive impairment
Adjusted for age, BMI, Education, energy(Quartiles),Hyperlipidemia

6. Please either explain your rationale for education grouping or add reference to it.
Answer: Thanks for your suggestion. In this study, we categorized the education level according to the following criteria:
≤ 6 years (illiterate, elementary school),
7~12 years (junior high school, senior high school, technical secondary school),
and > 12 years (college and graduate school).
We had included explanations for the education grouping and add a reference to it in the revised manuscript.(see page 6 line 54-58).

7. Please do the same for physical activity and add some more information regarding how the data was collected (i.e. questionnaire, pedometer etc).
Answer: Thanks for your suggestion. We collected the information of physical activities by questionnaire. We have explained this and added a reference in the revised manuscript (See page 6 Line 29-30 and page 7 line 15-18).

8. Dietary questionnaire Please add reference to FFQ used. Also, had this questionnaire been validated in this age group?
Answer: Thanks for your question. The FFQ used in the present study has been used to investigate nutrients intake by our team for many years and led to multiple publications, including
(1)Lu Y, An Y, Guo J, Zhang X, Wang H, Rong H and Xiao R. Dietary Intake of Nutrients and Lifestyle Affect the Risk of Mild Cognitive Impairment in the Chinese Elderly Population: A Cross-Sectional Study. Front. Behav. Neurosci. 2016;10:229. doi: 10.3389/fnbeh.2016.00229
(2)Yuan L, Liu J, Ma W1, Dong L, Wang W, Che R, Xiao R. Dietary pattern and antioxidants in plasma and erythrocyte in patients with mild cognitive impairment from China. Nutrition. 2016;32(2):193-8. doi: 10.1016/j.nut.2015.08.004.
(3)Dong L, Xiao R, Cai C, Xu Z, Wang S, Pan L, Yuan L.Diet, lifestyle and cognitive function in old Chinese adults. Arch Gerontol Geriatr. 2016;63:36-42. doi: 10.1016/j.archger.2015.12.003.
This FFQ has been validated in the age group of > 50. The present study was the first time that this FFQ is used in the age group of 30~65. Given the good performance of the FFQ in previous studies, we think it should be applicable to this age group to ensure the accuracy of the dietary survey. We also have added several references to this method in the revised manuscript (see page 7 line 22) ..

9. Cognitive function screening for MCI
Please make sure all abbreviations used have been explained/fully written the first time it appears in manuscript (apart from abstract), e.g. MoCA, MMSE
Answer: Thank you very much. We have double checked the whole manuscript, and explained all abbreviations when they appeared at the first time in the main text. The corrections in the manuscripts. (See page 4 line 12 and line 17-18, page 5 line 24, page 7 line 40, page 8 line 20-21)

10. Statistical analysis
Please be clear as to why categorical data was presented as mean or median.
Answer: Thank you for your suggestion. In this study we described the categorical variables as frequencies or percentages. This has been stated in the statistical analysis section that "Continuous variables were presented as mean and standard deviation (SD) or Median (Q), and categorical variables were described as frequencies (percentage)".

11. Results
please reword sentence on line 55-56 of page 6 as I am not sure if I understand it.
Answer: Thank you very much. This sentence was used as a transition and it was not necessary, so we have deleted this sentence.

12. Tables should have enough information to stand alone, this is not the case at the moment as there are several essential information missing in tables eg Table 1- race/ethnicity 'Han" and 'other'
Answer: Thank you for your valuable suggestions. Regarding the table 1, we have added explanations to the race groups, "Han" and "other". Han represent the main race of China, which accounts for about ninety percent of the Chinese population. Other included all other ethnicities except Han, such as Manchu, Hui and so on. We also double check other tables and added necessary explanations to make the tables have enough information to stand alone.

13. Table 2 – title should be more informative i.e. %fat in relation to what? Why are the groups divided into quartiles of %fat and %fat itself is also in the table?
Answer: Thank you for your valuable questions. We have revised the title of table 2 as Characteristics of Subjects by % fat Intake. We found that "%fat itself in the table" was a mistake, so we have deleted the column of "%fat/energy" in table 2.

VERSION 2 – REVIEW

REVIEWER	Rosilene Waern The University of Sydney
REVIEW RETURNED	26-Oct-2017

GENERAL COMMENTS	Thank you for your responses. I can see that your manuscript has improved significantly, however, I can still see some grammatical errors in the text. I advise having the manuscript revised again to improve the quality of the English throughout your manuscript. I would also suggest addressing the following: 1.Title needs to be reviewed, I would suggest "The Association between Macronutrients Intakes and cognition in individuals aged <65 in China. 2.Sentence "Mediterranean diet (MD)- rich in vegetables, fruit, fresh fish and olive oil -has been shown to have beneficial effects on cognitive function 3, 4 " – effects can only be shown in controlled trials, the references used are of epidemiological studies that can only show/suggest associations not effects.

	3.“A great number of previous studies have also demonstrated that adequate dietary intake of vitamins and minerals were closely associated with decreased risk of cognitive impairment” – you only gave one reference for this sentence, this is not a great number of studies, please revise. 4.Please avoid the use of the term “so on” as this is not informative enough. E.g. “Aerobic exercise15 refers to physical exercise of low to high intensity, including running/jogging, climbing, jumping rope, brisk walking, swimming, kicking shuttle cock and so on.

VERSION 2 – AUTHOR RESPONSE

Responses to Reviewer: 2
1. improve the quality of the English throughout your manuscript
Response: Our manuscript has edited by professional editors throughout the manuscript. We provided a CERTIFICATE OF ENGLISH EDITING following.

2. Title needs to be reviewed, I would suggest “The Association between Macronutrients Intakes and cognition in individuals aged <65 in China.

Response: Thank you very much! We have revised the title according to your and editor’s suggestion. And we realized it was more suitable for our manuscript than before one.
3. Sentence “Mediterranean diet (MD)- rich in vegetables, fruit, fresh fish and olive oil -has been shown to have beneficial effects on cognitive function 3, 4 “ – effects can only be shown in controlled trials, the references used are of epidemiological studies that can only show/suggest associations not effects.

Response: Thanks for your scientific and carefully review, we change the “effect” with “association” to make accurate expression.
4. “A great number of previous studies have also demonstrated that adequate dietary intake of vitamins and minerals were closely associated with decreased risk of cognitive impairment” – you only gave one reference for this sentence, this is not a great number of studies, please revise.

Response: Here we rewrite this sentence. Since there is only a quotation, we made some change in the beginning of the sentence.

5. Please avoid the use of the term “so on” as this is not informative enough.
E.g. “Aerobic exercise15 refers to physical exercise of low to high intensity, including running/jogging, climbing, jumping rope, brisk walking, swimming, kicking shuttle cock and so on.

Response: Thank you for your advice, we deleted “so on” in the whole manuscript.